Biolimus-eluting stents with biodegradable polymer versus bare-metal stents in acute myocardial infarction : Two-year clinical results of the COMFORTABLE AMI trial

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Abstract: BACKGROUND: This study sought to determine whether the 1-year differences in major adverse cardiac event between a stent eluting biolimus from a biodegradable polymer and bare-metal stents (BMSs) in the COMFORTABLE trial (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) were sustained during long-term follow-up. METHODS AND RESULTS: A total of 1161 patients were randomly assigned to biolimus-eluting stent (BES) and BMS at 11 centers, and follow-up rates at 2 years were 96.3%. A subgroup of 103 patients underwent angiography at 13 months. At 2 years, differences in the primary end point of cardiac death, target-vessel myocardial infarction, and target lesion revascularization continued to diverge in favor of BES-treated patients (5.8%) compared with BMS-treated patients (11.9%; hazard ratio = 0.48; 95% confidence interval, 0.31-0.72; P < 0.001) with a significant risk reduction during the second year of follow-up (hazard ratio 1-2 years = 0.45; 95% confidence interval, 0.20-1.00; P = 0.049). Differences in the primary end point were driven by a reduction in target lesion revascularization (3.1% versus 8.2%; P < 0.001) and target-vessel reinfarction (1.3% versus 3.4%; P = 0.023). The composite of death, any reinfarction and revascularization (14.5% versus 19.3%; P = 0.03), and cardiac death or target-vessel myocardial infarction (4.2% versus 7.2%; P = 0.036) were less frequent among BES-treated patients compared with BMS-treated patients. The 13-month angiographic in-stent percent diameter stenosis amounted to 12.0 ± 7.2 in BES- and 39.6 ± 25.2 in BMS-treated lesions (P < 0.001). CONCLUSIONS: Among patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention, BES continued to improve cardiovascular events compared with BMS beyond 1 year. CLINICAL TRIAL REGISTRATION URL: http://www.clinicaltrials.gov. Unique identifier: NTC00962416.

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Biolimus-Eluting Stents With Biodegradable Polymer Versus Bare-Metal Stents in Acute Myocardial Infarction

Two-Year Clinical Results of the COMFORTABLE AMI Trial

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Background—This study sought to determine whether the 1-year differences in major adverse cardiac event between a stent eluting biolimus from a biodegradable polymer and bare-metal stents (BMSs) in the COMFORTABLE trial (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) were sustained during long-term follow-up.

Methods and Results—A total of 1161 patients were randomly assigned to biolimus-eluting stent (BES) and BMS at 11 centers, and follow-up rates at 2 years were 96.3%. A subgroup of 103 patients underwent angiography at 13 months. At 2 years, differences in the primary end point of cardiac death, target-vessel myocardial infarction, and target lesion revascularization continued to diverge in favor of BES-treated patients (5.8%) compared with BMS-treated patients (11.9%; hazard ratio=0.48; 95% confidence interval, 0.31–0.72; $P<0.001$) with a significant risk reduction during the second year of follow-up (hazard ratio 1–2 years=0.45; 95% confidence interval, 0.20–1.00; $P=0.049$). Differences in the primary end point were driven by a reduction in target lesion revascularization (3.1% versus 8.2%; $P<0.001$) and target-vessel reinfarction (1.3% versus 3.4%; $P=0.023$). The composite of death, any reinfarction and revascularization (14.5% versus 19.3%; $P=0.03$), and cardiac death or target-vessel myocardial infarction (4.2% versus 7.2%; $P=0.036$) were less frequent among BES-treated patients compared with BMS-treated patients. The 13-month angiographic in-stent percent diameter stenosis amounted to 12.0±7.2 in BES- and 39.6±25.2 in BMS-treated lesions ($P<0.001$).

Conclusions—Among patients with ST-segment–elevation myocardial infarction undergoing primary percutaneous coronary intervention, BES continued to improve cardiovascular events compared with BMS beyond 1 year.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NTC00962416.

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Key Words: angiography ■ drug-eluting stents ■ myocardial infarction

Primary percutaneous coronary intervention (PCI) is the reperfusion therapy of choice for patients with acute ST-segment–elevation myocardial infarction (STEMI).[1,2] Early-generation drug-eluting stents (DES) have been shown more effective than bare-metal stents (BMS), but they were associated with an increased risk of very late stent thrombosis (ST).[3] Polymers components applied to the stent surface to enable delayed drug release have been implicated in the pathogenesis of delayed arterial healing and vessel remodeling owing to chronic inflammation. More recently, new-generation DESs with more biocompatible durable and biodegradable polymers have largely overcome this limitation, although the long-term safety profile of these devices particularly among patients with STEMI has not been established to date.

Biolimus-eluting stents (BES) are new-generation DES with biodegradable polymer for drug release, which is resorbed

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WHAT IS KNOWN

- Among patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention, biodegradable polymer biolimus-eluting stents reduce major cardiovascular events compared with bare-metal stents at 1 year.
- The clinical effect of newer generation biodegradable drug-eluting stent beyond 1 year after primary percutaneous coronary intervention is unknown.

WHAT THE STUDY ADDS

- Biolimus-eluting stent is associated with a continued reduction of major cardiovascular events during the second year of follow-up.
- Clinical differences were not only driven by a difference in efficacy but also by ischemic end points including cardiac death or target-vessel myocardial infarction.
- Although 60% patients discontinued dual antiplatelet therapy at 1 year, no difference in very late stent thrombosis was observed between biodegradable drug-eluting stent and bare-metal stents.

during a period of 6 to 9 months. In an all comers trial,[4] a significant reduction of very late ST vis-à-vis a durable polymer–based early-generation sirolimus-eluting stent was observed during long-term follow-up. A dedicated randomized trial in patients with STEMI comparing BES with BMS of otherwise identical design showed a reduction in major adverse cardiac events (MACEs) at 1 year owing to a lower risk of target-lesion revascularization and target-vessel myocardial infarction.[5] Whether the clinical benefits of BES over BMS remain sustained during long-term follow-up is unknown. The purpose of this study is to report the long-term clinical outcome of patients included in Comparison of Biolimus Eluted from an Erodible Stent Coating with Bare-Metal Stents in Acute ST-Elevation Myocardial Infarction (COMFORTABLE AMI) trial throughout 2 years and the results of the angiographic substudy performed 13 months after stent implantation (see the Data Supplement for a list of investigators).

Methods

Study Design

The study design of COMFORTABLE AMI trial has been reported elsewhere.[5,6] Briefly, this is a multicenter, randomized, assessor-blind, superiority trial in patients with STEMI undergoing primary PCI registered at ClinicalTrials.gov (NTC00962416). Consecutive patients ≥18 years with acute ST-segment elevation of ≥1 mm in ≥2 contiguous leads, true posterior myocardial infarction, or new left bundle branch block were eligible for randomization in the presence of ≥1 culprit lesion within the infarct vessel. There was no limit about the number of treated lesions, vessels, or complexity. Exclusion criteria were presence of mechanical complications of acute myocardial infarction, known allergy to any study medication, use of vitamin K-antagonists, planned surgery unless dual antiplatelet therapy could be maintained throughout the perisurgical period, history of bleeding diathesis or known coagulopathy, pregnancy, participation in another trial before reaching the primary end point, inability to provide informed consent, and noncardiac comorbid conditions with life expectancy below 1 year. The study complied with the declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written, informed consent.

Procedures

Randomization was performed via a Web-based system after diagnostic angiography. Patients were randomly assigned 1:1 to treatment with stents eluting biolimus from a biodegradable polylactic acid polymer (BioMatrix; Biosensors Europe SA, Morges, Switzerland) or BMSs of otherwise identical design (Gazelle; Biosensors Europe SA, Morges, Switzerland). Before stent implantation, thrombus aspiration was recommended whenever aspiration was deemed technically feasible. Predilatation of the culprit lesion was left to the discretion of the operator. Complete revascularization of all lesions within the infarct vessel had to be performed with the randomly allocated study stent. Acetylsalicylic acid (≥250 mg) was given before the procedure. In centers where prasugrel was available, an initial dose of 60 mg (including patients preloaded with clopidogrel) was given followed by a daily dose of 10 mg. If prasugrel was not available or contraindicated, clopidogrel was administered at a loading dose of 600 mg, followed by a dose of 75 mg twice daily for 7 days followed by a maintenance dose of 75 mg once daily. Dual antiplatelet therapy was prescribed for the duration of ≥1 year in all patients. During the procedure, unfractionated heparin was given at a dose of at least 5000 international units or 70 to 100 international units/kg or alternatively bivalirudin. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator.

Data Management and Clinical End Points

Independent study monitors verified source data according to a prespecified monitoring plan.[5] Data were stored in a central database (Cardiobase, Clinical Trials Unit and Department of Cardiology, Bern University Hospital, Switzerland and 2mT, Ulm, Germany). Follow-ups were scheduled at 30 days and 1 and 2 years, and patients were questioned about the occurrence of angina, any adverse events, recurrent hospitalizations, and cardiovascular medication intake. Any death, reinfarction, revascularization, ST, cerebrovascular accident, and bleeding event were independently adjudicated by a blinded clinical event committee. The prespecified primary end point was the device-oriented composite of cardiac death, target-vessel reinfarction, and ischemia-driven target-lesion revascularization within 12 months. Detailed definitions of all primary and secondary end points were reported elsewhere.[7]

Angiographic Substudy

Five participating centers were selected as intracoronary imaging centers and recruited patients into the formal angiographic and intracoronary imaging substudy (Bern, Copenhagen, Geneva, Lugano, and Zurich). Patients enrolled in the COMFORTABLE AMI study were eligible for participating the angiographic substudy when the following criteria were fulfilled: age <90 years, hemodynamic stability, preserved renal function (glomerular filtration rate >30 mL/min), thrombolysis in myocardial infarction flow ≥II of the infarct-related artery at the end of the intervention, coronary anatomy suitable for intracoronary imaging, and agreement to undergo angiographic and intracoronary imaging follow-up at 13 months. All patients were scheduled for repeat angiography of the culprit lesion at 13 months after recording of the primary clinical outcome. Coronary angiograms were recorded at baseline immediately after the procedure and at 13 months and were assessed at the core laboratory of Bern University Hospital. Patients received nitroglycerin before angiography, and measurements were performed on cineangiograms. The contrast-filled, untapered tip of the catheter was used for calibration. Quantitative measurements included reference vessel diameter, minimal lumen diameter, and percent diameter stenosis. Digital angiograms were analyzed with the use of the software (QAngio XA Version 7.1; Medis, Leiden, The Netherlands). Quantitative coronary angiograms from patients returning for repeat angiography in the setting of ST were not included during the first 30 days.

Statistical Analysis

COMFORTABLE AMI trial was powered for superiority on the primary clinical end point at 1 year. All analyses were performed according to the intention-to-treat principle, with inclusion of all 1161 randomized patients in the analysis according to the originally allocated stent type. Medication intake at discharge and follow-up was reported as counts and percentages, and groups were compared using Fisher exact tests. Cox proportional hazards models were used to compare clinical outcomes between the allocated stents, with patients censored at the time of their last valid contact. Landmark Cox proportional hazards models were used to compare clinical outcomes between the allocated stents in different periods since PCI; the *P* value for the interaction compares the period before (eg, 30 days or 1 year) to the period after the landmark (eg, beyond 30 days or 1 year) using robust variance estimators. Analyses for MACE were repeated excluding the subgroup of patients enrolled in the COMFORTABLE Imaging substudy. All *P* values are 2-sided, and all analyses were performed with Stata 12.1. The sample size of the imaging subgroup was calculated to show superiority of BES over BMS in terms of neointimal thickness as assessed by optical coherence tomography (not reported here).

Table 1. Baseline and Procedural Characteristics

Patients	Biolimus-Eluting Stents (n=575)	Bare-Metal Stents (n=582)	*P* Value
Age, y	60.7±11.6	60.4±11.9	
Male sex, n (%)	463 (80.5)	455 (78.2)	
Body mass index, kg/m^2	27.3±4.5	27.2±4.0	
Cardiovascular risk factors			
Diabetes mellitus, n (%)	84 (14.6)	90 (15.5)	
Hypertension, n (%)	279 (48.5)	265 (45.5)	
Hyperlipidemia, n (%)	324 (56.6)	328 (56.7)	
Current smoker, n (%)	272 (47.9)	301 (52.3)	
Family history of CAD, n (%)	193 (34.3)	179 (31.3)	
Clinical presentation			
Time from symptom onset to balloon inflation, min (IQR)	232 (164–380)	236 (163–400)	
0–6 h	421 (73.2)	421 (72.6)	
6–12 h	109 (19.0)	100 (17.2)	
12–24 h	45 (7.8)	59 (10.2)	
Time from hospital admission to balloon inflation, min (IQR)	44 (32–70)	44 (32–74)	
Killip class II, III, or IV, n/total n (%)	40 (7.0)	37 (6.4)	
Left ventricular ejection fraction, %	49±11	50±10	
Lesion complexity			
Bifurcation lesion, n (%)	52 (9.0)	49 (8.4)	
Small vessel (reference vessel diameter ≤2.5 mm)	74 (12.9)	79 (13.7)	
Long lesion (lesion length ≥20 mm)	204 (35.7)	183 (31.7)	
SYNTAX MI score	15.1±8.2	14.8±8.1	
Lesions treated in infarct vessel, n	629	648	
Lesions treated per patient	1.1±0.3	1.1±0.4	0.61
Baseline TIMI flow, n (%)			0.31
0 or 1	437 (69.6)	423 (65.6)	
2	81 (12.9)	95 (14.7)	
3	110 (17.5)	127 (19.7)	
Primary PCI procedure			
No. of stents per lesion	1.32±0.61	1.26±0.60	0.16
Stent length per lesion, mm	25.2±12.7	24.1±12.3	0.10
Stent diameter per lesion, mm	3.2±0.4	3.2±1.1	0.42
Direct stenting, n (%)	236 (37.6)	240 (37.3)	0.89
Maximal balloon pressure, atm	15.2±3.5	15.1±3.4	0.50
Thrombus aspiration, n (%)	350 (60.9)	374 (64.4)	0.22
Final TIMI flow, n (%)			
0 or 1	3 (0.5)	3 (0.5)	0.70
2	25 (4.0)	32 (5.0)	
3	601 (95.5)	611 (94.6)	

CAD indicates coronary artery disease; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; and TIMI, thrombolysis in myocardial infarction.

Results

A total of 1161 patients were randomly assigned to receive BES with biodegradable polymer (578 patients) or BMS (583 patients). Follow-up at 2 years was available in 96.7% of BES-treated patients and 95.9% of BMS-treated patients. Baseline clinical and procedural characteristics were well balanced in both stent groups (Table 1). Compliance with recommended durations of dual antiplatelet therapy is summarized in Table 2. Per protocol, dual antiplatelet therapy with either clopidogrel or prasugrel was recommended for ≥1 year. We observed no differences in dual antiplatelet therapy compliance at any time point, and ≈18% of patients in both groups remained on thienopyridines throughout 2 years. No differences about the type of thienopyridine were noted between groups at any time point.

Clinical Outcomes During Long-Term Clinical Follow-Up

Long-term clinical outcomes are summarized in Table 3. At 2 years, the primary end point of MACEs (cardiac death, target-vessel reinfarction, and ischemia-driven target-lesion revascularization) occurred in 5.8% of patients receiving BES and 11.9% of patients receiving BMS (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.31–0.72; *P*<0.001) (Figure 1A). Individual components of the primary end point showed significant differences in favor of BES for target-vessel reinfarction (1.3% versus 3.4%; HR, 0.37; 95% CI, 0.15–0.87; *P*=0.023) and ischemia-driven target-lesion revascularization (3.1% versus 8.2%; HR, 0.36; 95% CI, 0.21–0.63; *P*<0.001) (Figure 1B–1D). The patient-oriented composite end point of all-cause death, any reinfarction, and any revascularization was observed in 14.5% among BES-treated patients with STEMI and 19.3% of BMS-treated patients with STEMI (HR, 0.73; 95% CI, 0.55–0.97; *P*=0.03). Cardiac death or target-vessel reinfarction was lower among patients receiving BES (4.2%) compared with patients receiving BMS (7.2%; HR, 0.58; 95% CI, 0.35–0.97; *P*=0.036) at 2 years. Rates of definite or definite and probable ST are shown in Figure 2 and were numerically but not statistically lower with BES compared with BMS at 2 years.

Clinical Outcomes Beyond 1 Year of Follow-Up

Clinical outcomes between 1 and 2 years are summarized in Table 2 and Figure 3. The landmark analysis at 1 year shows that differences between stent types in terms of the primary end point MACE continued to favor patients treated with BES (1.7% versus 3.7%; HR, 0.45; 95% CI, 0.20–1.00; *P*=0.049) without evidence of interaction between the 2 time periods ($P_{interaction}$=0.88). A sensitivity analysis excluding patients undergoing repeat angiography at 13 months showed a consistent benefit of BES over BMS during the second year of follow-up ($HR_{1\text{-}2\ years}$, 0.45; 95% CI, 0.20–1.0; *P*=0.049). Differences between stent types were not significant for cardiac death, target-vessel reinfarction, and ischemia-driven target-lesion revascularization, although event rates were numerically lower for BES than BMS between 1 and 2 years. There were no differences in rates of very late definite (BES 0.6% versus BMS 0.4%; HR, 1.47; 95% CI, 0.25–8.83; *P*=0.67) and very late definite or probable ST (BES 0.8% versus BMS 0.8%; HR, 0.98; 95% CI, 0.25–3.93; *P*=0.98).

Angiographic Results

A total of 103 patients were included into the angiographic substudy, and the results are shown in Table 4. Only few patients

Table 2. Dual Antiplatelet Therapy Intake Throughout 2 Years

	Biolimus-Eluting Stents (n=575)	Bare-Metal Stents (n=582)	*P* Value
At discharge, n (%)	n=569	n=578	
Acetylsalicylic acid	568 (99.8%)	576 (99.7%)	1.00
Clopidogrel	323 (56.8%)	327 (56.6%)	0.95
Prasugrel	245 (43.1%)	248 (42.9%)	1.00
Any dual antiplatelet therapy	567 (99.6%)	574 (99.3%)	0.69
At 30 d, n (%)	n=560	n=570	
Acetylsalicylic acid	556 (99.3%)	565 (99.1%)	1.00
Clopidogrel	323 (57.6%)	322 (56.5%)	0.72
Prasugrel	240 (42.9%)	245 (43.0%)	1.00
Any dual antiplatelet therapy	554 (98.9%)	559 (98.1%)	0.33
At 1 y, n (%)	n=543	n=545	
Acetylsalicylic acid	530 (97.6%)	525 (96.3%)	0.29
Clopidogrel	287 (52.9%)	266 (48.8%)	0.18
Prasugrel	213 (39.2%)	223 (40.9%)	0.58
Any dual antiplatelet therapy	490 (90.2%)	479 (87.9%)	0.24
At 2 y, n (%)	n=530	n=525	
Acetylsalicylic acid	511 (96.4%)	498 (94.9%)	0.23
Clopidogrel	71 (13.4%)	59 (11.2%)	0.30
Prasugrel	29 (5.5%)	40 (7.6%)	0.17
Any dual antiplatelet therapy	93 (17.5%)	93 (17.7%)	1.00

Table 3. Clinical Outcomes at 2 Years and Between 1 and 2 Years

	Biolimus-Eluting Stents (n=575)	Bare-Metal Stents (n=582)	Hazard Ratio (95% CI)	*P* Value
All events at 2 y				
Death	28 (4.9%)	32 (5.6%)	0.79 (0.53–1.46)	0.62
Cardiac death	17 (3.0%)	25 (4.4%)	0.69 (0.37–1.27)	0.23
Reinfarction	18 (3.3%)	28 (5.0%)	0.64 (0.35–1.16)	0.14
Q-wave	6 (1.1%)	9 (1.6%)	0.67 (0.24–1.88)	0.45
Non–Q-wave	12 (2.2%)	19 (3.4%)	0.63 (0.31–1.30)	0.21
Target-vessel reinfarction	7 (1.3%)	19 (3.4%)	0.37 (0.15–0.87)	0.023
Q-wave	4 (0.7%)	8 (1.4%)	0.50 (0.15–1.67)	0.26
Non–Q-wave	3 (0.6%)	11 (2.0%)	0.27 (0.08–0.98)	0.046
Cardiac death or target-vessel reinfarction	24 (4.2%)	41 (7.2%)	0.58 (0.35–0.97)	0.036
Any TLR	19 (3.5%)	53 (9.5%)	0.35 (0.21–0.59)	<0.001
Ischemia-driven TLR	17 (3.1%)	46 (8.2%)	0.36 (0.21–0.63)	<0.001
Any TVR	26 (4.7%)	58 (10.4%)	0.44 (0.27–0.69)	<0.001
Ischemia-driven TVR	23 (4.2%)	51 (9.1%)	0.44 (0.27–0.72)	0.001
Major adverse cardiac events*	33 (5.8%)	68 (11.9%)	0.48 (0.31–0.72)	<0.001
Death, any reinfarction, any revascularization	82 (14.5%)	110 (19.3%)	0.73 (0.55–0.97)	0.03
Stroke	6 (1.6%)	4 (1.1%)	1.51 (0.54–4.25)	0.43
Definite stent thrombosis	8 (1.4)	15 (2.6)	0.53 (0.23–1.26)	0.15
Definite or probable stent thrombosis	18 (3.2%)	25 (4.4%)	0.72 (0.39–1.32)	0.29
All events between 1 and 2 y				
Death	10 (1.9%)	9 (1.7%)	1.11 (0.45–2.73)	0.82
Cardiac death	1 (0.2%)	5 (0.9%)	0.20 (0.02–1.71)	0.14
Reinfarction	7 (1.3%)	7 (1.4%)	0.99 (0.35–2.82)	0.98
Q-wave	4 (0.7%)	2 (0.4%)	1.99 (0.36–10.87)	0.43
Non–Q-wave	3 (0.6%)	5 (1.0%)	0.59 (0.14–2.48)	0.48
Target-vessel reinfarction	4 (0.8%)	4 (0.8%)	0.98 (0.25–3.92)	0.98
Q-wave	3 (0.6%)	1 (0.2%)	2.98 (0.31–28.64)	0.35
Non–Q-wave	1 (0.2%)	3 (0.6%)	0.33 (0.03–3.15)	0.33
Cardiac death or target-vessel reinfarction	5 (0.9%)	9 (1.7%)	0.55 (0.18–1.63)	0.28
Any TLR	24 (4.7%)	31 (6.3)	0.74 (0.44–1.27)	0.27
Ischemia-driven TLR	8 (1.5%)	14 (2.7)	0.55 (0.23–1.30)	0.17
Any TVR	15 (2.9%)	21 (4.1)	0.68 (0.35–1.32)	0.25
Ischemia-driven TVR	12 (2.3%)	16 (3.1)	0.72 (0.34–1.52)	0.39
Major adverse cardiac events*	9 (1.7%)	19 (3.7%)	0.45 (0.20–1.00)	0.049
Death, any reinfarction, any revascularization	35 (6.9%)	41 (8.3%)	0.82 (0.52–1.29)	0.39
Stroke	3 (0.6%)	2 (0.4%)	1.51 (0.25–9.02)	0.65
Definite stent thrombosis	3 (0.6%)	2 (0.4%)	1.47 (0.25–8.83)	0.67
Definite or probable stent thrombosis	4 (0.8%)	4 (0.8%)	0.98 (0.25–3.93)	0.98

Data are number of patients (%). Hazard ratios are derived from Cox proportional hazard models. *P* values are 2-sided from superiority testing with a χ^2 test. CI indicates confidence interval; TLR, target lesion revascularization; and TVR, target vessel revascularization.

*It is a composite of cardiac death, target-vessel reinfarction, and ischemia-driven target-lesion revascularization.

of the angiographic cohort did not undergo protocol-mandated follow-up angiography at 13 months (13.2% for BES- and 10% for BMS-treated patients). Reference vessel diameter and minimal lumen diameter were comparable in both groups after the procedure. At 13-month follow-up, percent diameter stenosis (in-stent, 12.02±7.23 versus 39.60±25.21; in-segment, 21.55±8.70 versus 41.29±24.10 mm) and in-segment (0.10±0.30 versus 0.71±0.75 mm; *P*<0.001) and in-stent late lumen loss (0.10±0.24 versus 0.97±0.75 mm, *P*<0.001) were lower in BES-treated lesion compared with BMS-treated lesions. As a result, there was a large difference in in-segment binary restenosis (0% versus 25.9%; *P*<0.001). The cumulative distribution of % diameter stenosis stratified by stent type is shown in Figure 4.

Discussion

This study reports long-term clinical outcomes of new-generation DES with biodegradable polymer compared with BMS

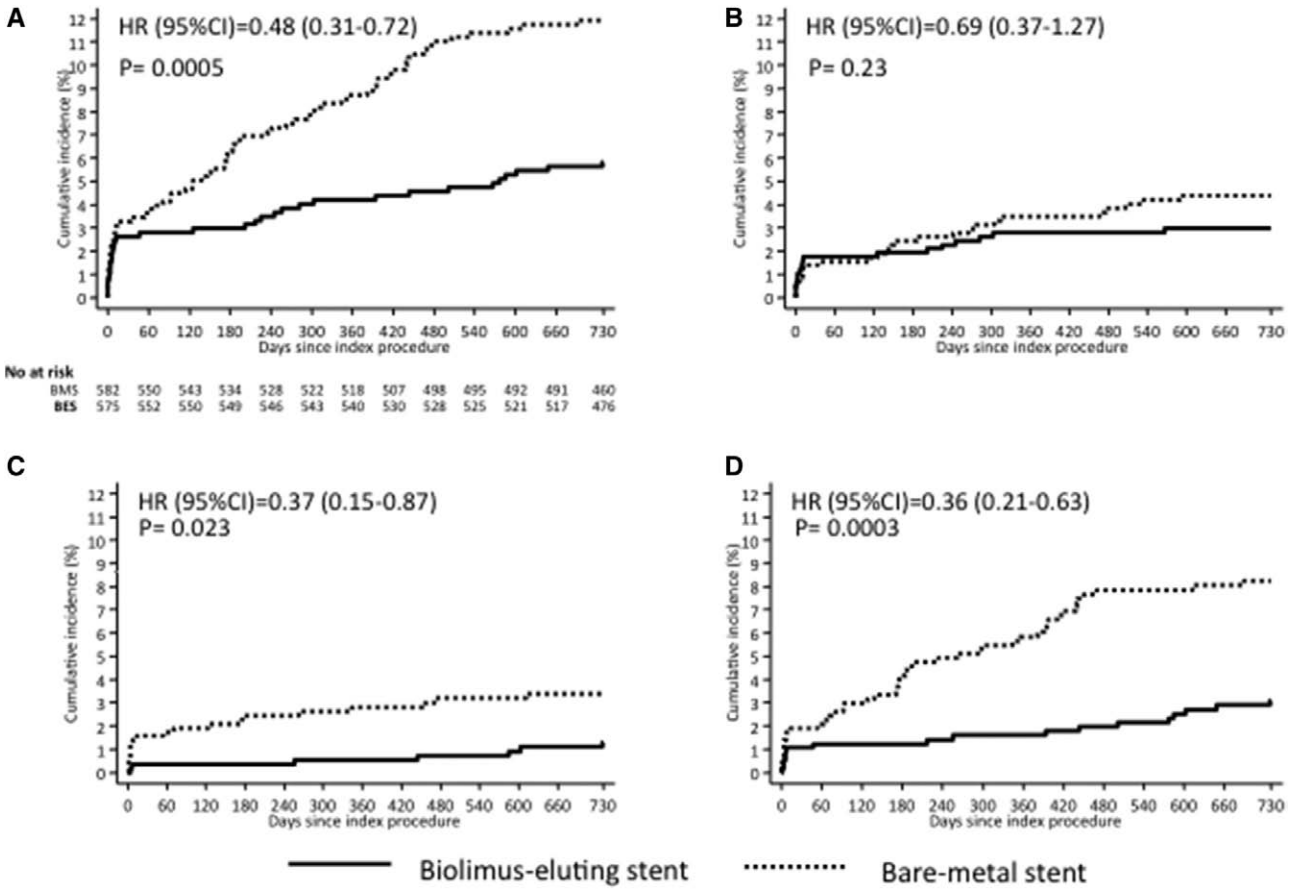

Figure 1. Time-to-event curves for the primary end point of major adverse cardiac events (composite of cardiac death, target-vessel–related reinfarction, and ischemia-driven target-lesion revascularization) throughout 2 years (**A**), cardiac death (**B**), target-vessel–related reinfarction (**C**), and ischemia-driven target-lesion revascularization (**D**) for patients receiving biolimus-eluting stents with biodegradable polymer and patients receiving bare-metal stents. *P* values are 2-sided from Cox regression models χ^2 test. CI indicates confidence interval; and HR, hazard ratio.

among patients with STEMI undergoing primary PCI with the following principal findings:

1. At 2 years, BES significantly reduced the risk of the device-oriented composite of cardiac death, target-vessel myocardial infarction (TV-MI), ischemia-driven target lesion revascularization (TLR), and the patient-oriented composite of death, any reinfarction, and any repeat revascularization.
2. The benefit of BES over BMS in terms of major cardiovascular events was not only sustained but also continued to accrue beyond 1 year of clinical follow-up.
3. At 2 years, BES was associated with a significantly reduced risk of cardiac death or TV-MI and a reduced risk for the individual components of the primary end point including TV-MI and ischemia-driven TLR.
4. Very late ST occurred with similar frequency among BES- and BMS-treated patients beyond 1 year.
5. Compared with BMS, BES potently suppressed neointimal hyperplasia resulting in a lower risk of restenosis.

A key finding of this study is the continued benefit of DES over BMS in the prevention of MACEs during the time period beyond 1 year. Indeed, the clinical benefit of BES over BMS estimated as numbers needed to treat to prevent 1 MACE amounted to 24 at 1 year but further decreased to 13 at 2 years of follow-up suggesting continued clinical benefit. Of note, the improved outcomes at 2 years in terms of the composite primary end point of MACEs were not only driven by expected differences in efficacy but also extended to ischemic end points including a lower risk for the composite of cardiac death or TV-MI as well as TV-MI, a finding which has not been previously observed in STEMI trials comparing early-generation DES with BMS.[8,9]

The continued reduction in major cardiovascular events between the first and second of follow-up in favor of BES warrants discussion because the biodegradable polymer–based DES should theoretically have turned into a metallic bare stent with similar properties as BMS. The performance of a repeat angiography in 8% of the overall study population did not significantly impact the outcome as evidenced in a sensitivity analysis. Although data from angiographic follow-up studies indicate that most restenotic events leading to repeat revascularization occur between 6 and 12 months with BMS, the numerically higher event rate in terms of TLR in this study speaks to the fact that delayed restenosis beyond 1 year may be more pronounced with BMS than BES. However, it remains speculative why the reduced risk of TLR beyond 1 year was accompanied by numerically lower events rates for cardiac death and myocardial infarction because there were no differences in terms of definite or probable ST.

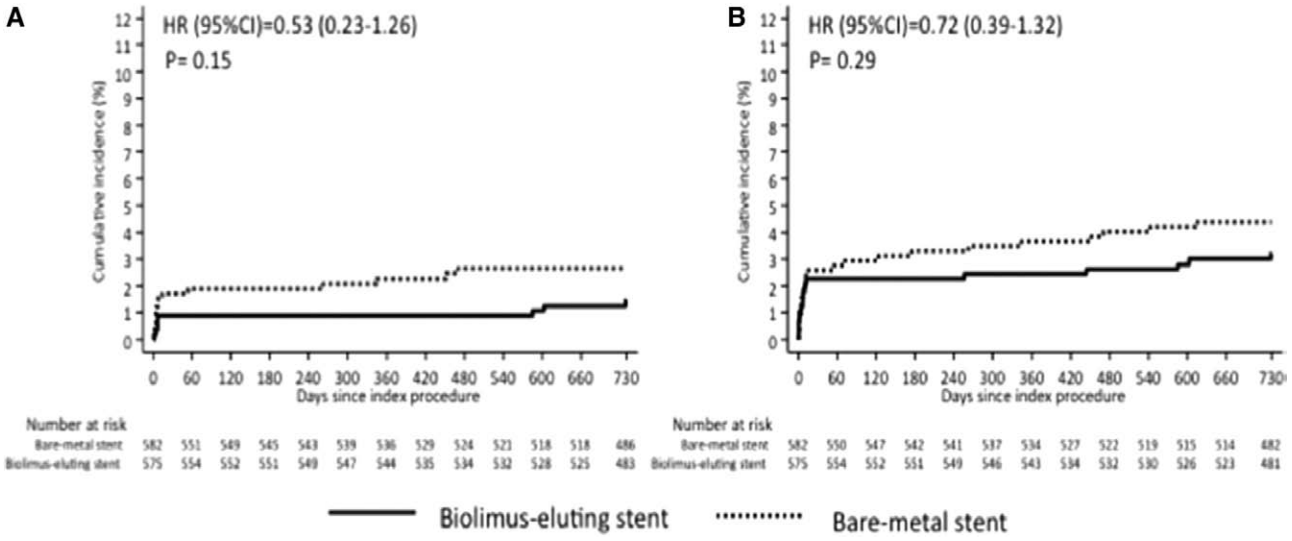

Figure 2. Time-to-event curves for definite (**A**) and definite or probable (**B**) stent thrombosis throughout 2 years. CI indicates confidence interval; and HR, hazard ratio.

BES was also associated with a lower risk of the primary end point MACE (a composite of cardiac death, myocardial infarction, and clinically indicated TLR) compared with sirolimus-eluting stent–treated patients (BES 6.7% versus sirolimus-eluting stent 15.7%; HR, 0.40; 95% CI, 0.18–0.87; *P*=0.02) in the STEMI subgroup of patients enrolled into the BES With Biodegradable Polymer Versus Sirolimus-Eluting Stent With Durable Polymer for Coronary Revascularization (LEADERS) trial. The favorable treatment effect of BES over sirolimus-eluting stent observed in the STEMI subgroup of the LEADERS

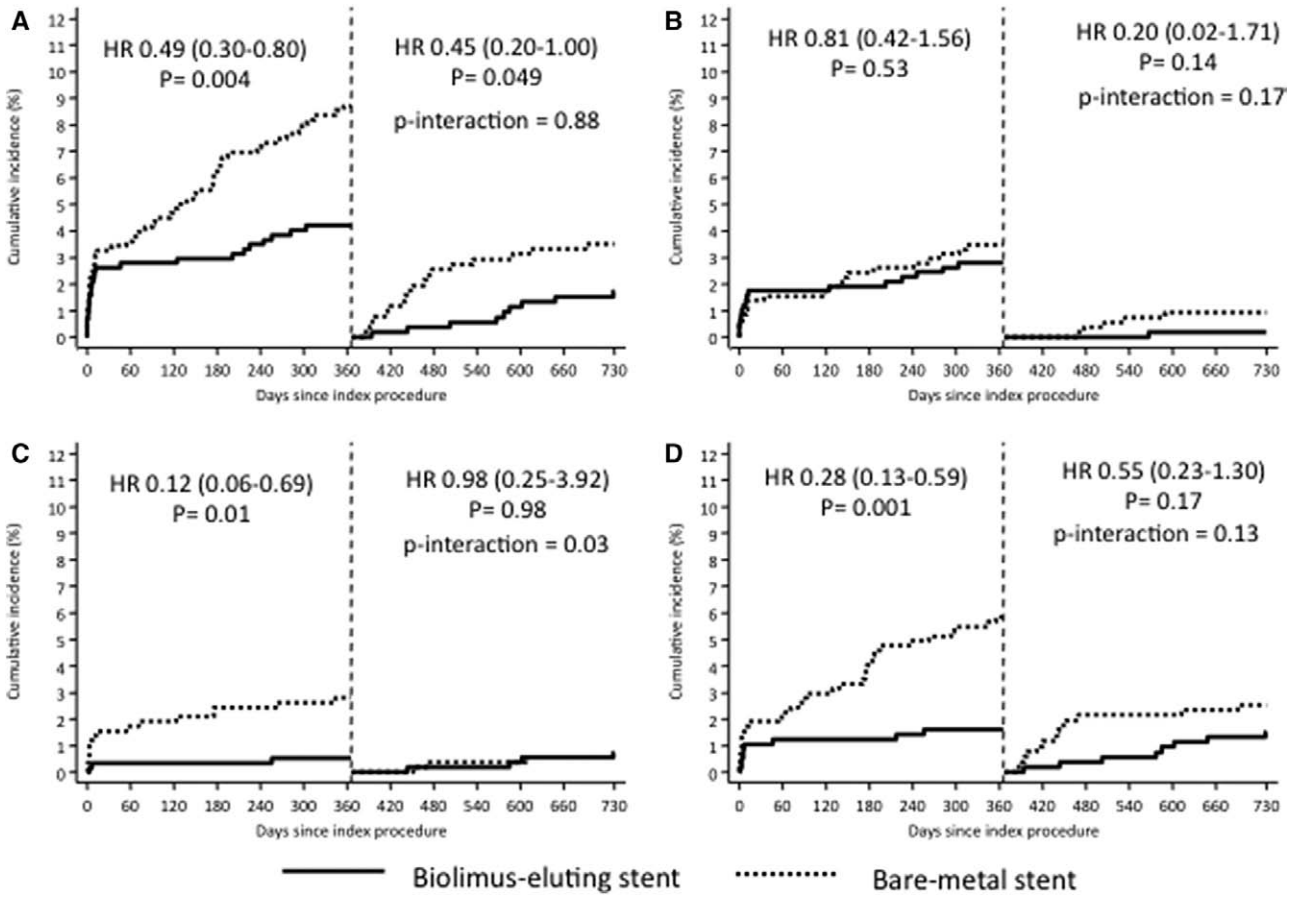

Figure 3. Time-to-event curves for the primary end point of major adverse cardiac events throughout 2 years with landmark analysis at 1 year (**A**), cardiac death (**B**), target-vessel–related reinfarction (**C**), and ischemia-driven target-lesion revascularization (**D**) for patients receiving biolimus-eluting stents with biodegradable polymer and patients receiving bare-metal stents. *P* values for interaction are for differences in hazard ratios between 0 to 1 and 1 to 2 years. HR indicates hazard ratio.

Table 4. Angiographic Results

	Biolimus-Eluting Stents	BMS	Difference (95% CI)*	*P* Value†
No. of patients	53	50		
No. of lesions	62	59		
Preprocedural				
Reference vessel diameter, mm	3.05±0.51	3.00±0.44	0.05 (–0.12 to 0.22)	0.57
Minimal lumen diameter, mm	0.52±0.57	0.48±0.59	0.04 (–0.17 to 0.25)	0.70
Lesion length, mm	15.59±7.99	17.19±9.54	–1.60 (–4.76 to 1.57)	0.32
Diameter stenosis, %	82.78±18.64	83.75±19.76	–0.97 (–7.88 to 5.94)	0.78
Postprocedural				
Reference vessel diameter, mm	3.08±0.57	3.06±0.48	0.02 (–0.17 to 0.21)	0.85
Minimal lumen diameter, mm				
In-stent	2.83±0.53	2.77±0.39	0.07 (–0.10 to 0.23)	0.43
In-segment	2.48±0.48	2.43±0.50	0.05 (–0.12 to 0.23)	0.55
Diameter stenosis, %				
In-stent	9.04±4.61	10.30±5.03	–1.26 (–3.00 to 0.47)	0.15
In-segment	18.39±9.11	20.48±10.80	–2.08 (–5.68 to 1.51)	0.25
13-mo follow-up‡				
No. of patients FUP	46	45		
No. of lesions FUP	54	54		
Reference vessel diameter, mm	3.07±0.61	2.92±0.52	0.15 (–0.06 to 0.37)	0.16
Minimal lumen diameter, mm				
In-stent	2.73±0.57	1.79±0.83	0.94 (0.67 to 1.21)	<0.001
In-segment	2.37±0.47	1.75±0.80	0.62 (0.37 to 0.87)	<0.001
Diameter stenosis, %				
In-stent	12.02±7.23	39.60±25.21	–27.58 (–34.65 to –20.52)	<0.001
In-segment	21.55±8.70	41.29±24.10	–19.74 (–26.65 to –12.84)	<0.001
Binary stenosis, %				
In-stent	0 (0.00%)	14 (25.93%)	–25.93 (–37.84 to –14.01)	<0.001§
In-segment	0 (0.00%)	14 (25.93%)	–25.93 (–37.84 to –14.01)	<0.001§
Late loss, mm				
In-stent	0.11±0.24	0.97±0.75	–0.87 (–1.08 to –0.65)	<0.001
In-segment	0.10±0.30	0.71±0.75	–0.61 (–0.83 to –0.39)	<0.001

BMS indicates bare-metal stent; CI, confidence interval; and FUP, follow-up.
*Crude difference biolimus-eluting stent (BES) vs BMS overall across all lesions (95% CI).
†Mixed model *P* values accounting for lesions nested within patient identifier.
‡Two patients (n=1 BES; n=1 BMS) who presented with definite stent thrombosis within 30 d were excluded from the follow-up 13-mo quantitative coronary analysis.
§All BES lesions without binary stenosis: Fisher test on culprit lesion only.

trial provides further support for the clinical benefit observed with BES in our trial. Extended follow-up beyond 1 year among patients with STEMI undergoing primary PCI is clinically important to assess the long-term safety profile of DES particularly at the time after discontinuation of the routinely recommended 12-month duration of dual antiplatelet therapy. Previous studies did suggest an increased risk of very late ST and TV-MI beyond 1 year in patients treated with early-generation DES.[8,9] We, therefore, performed detailed analyses using landmark techniques set at 1 year to gain insights into the risk profile and potential mechanisms of action of biodegradable polymer DES compared with BMS. Although there were no differences in cardiac death, BES showed a significant interaction with time in terms of TV-MI, namely a reduced risk of TV-MI, compared with BMS during the first year risk reduction=80%) followed by a similar risk (risk reduction=2%) during the subsequent year of follow-up. The similar rather than increased risk of TV-MI associated with BES compared with BMS beyond 1 year is noteworthy because it differs from the previous experience with early-generation DES. It is explained at least in part by the optimized polymer-drug profile characterized by early drug release followed by biodegradation of the polylactid acid polymer resulting in a surface similar to a BMS platform after a period of 6 to 9 months. In addition, the antiproliferative drug does not only suppress neointimal proliferation thereby preventing TV-MI due to restenosis but may also exert an antithrombotic effect in concert with the polymer,[10] which is hypothetically more relevant in the hypercoagulable milieu of patients with STEMI.[11]

Similar to the risk of TV-MI, we observed a trend toward a lower rate of ST with BES during the first year, followed by the absence of differences in very late definite and definite or

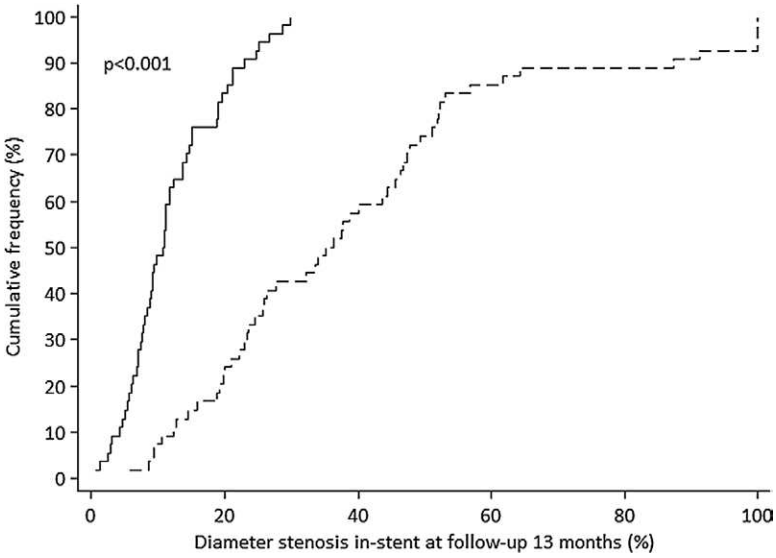

Figure 4. Cumulative distribution curve for angiographic percent diameter stenosis comparing biolimus-eluting stents vs bare-metal stents at 13-mo follow-up.

probable ST beyond 1 year. Nevertheless, very late ST was not eliminated as indicated by a residual rate of 0.6% for BES-treated patients and 0.4% for BMS-treated patients during the second year of follow-up. In Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZON AMI) trial,[12] the rate of very late ST was 1.1% among paclitaxel-eluting stents and 0.6% among BMS-treated patients during the second year of follow-up. The 2-year results of the everolimus-eluting stent (EES) versus BMS in ST-segment–elevation myocardial infarction (EXAMINATION)[13] trial comparing EES with BMS in patients with STEMI are consistent with this study, specifically, there was no difference in very late ST (EES 0.3% versus BMS 0.3%). Although EES in the setting of STEMI did not result in a lower risk of TV-MI, they were associated with a significant reduction in definite ST at 2 years (EES 0.8% versus BMS 2.1%; P=0.03). Although in the EXAMINATION trial, BMS-treated patients showed a significantly higher discontinuation of dual antiplatelet therapy at 1 year (90%) compared with EES-treated patients (98%, P<0.001), numbers were comparable between treatment arms at 2 years (EES and BMS 18%) in both trials.

The similar safety profile of BES and BMS beyond 1 year is supported by the fact that ≈60% of patients in both treatment groups discontinued routine dual antiplatelet therapy at 13 months and 82% at 2 years. Although observational in nature, the results of this study suggest that discontinuation of P2Y12 inhibitors at 1 year may be reasonable among patients with STEMI.

Compared with BMS, BES reduced the risk of TLR by 72% during the first year, whereas no significant reduction was observed during the second year. The angiographic results obtained at 13 months in the subgroup of 103 patients revealed a late lumen loss, which was similar to the one observed in the angiographic substudy of the biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularization (LEADERS)[4] trial assessed at 9 months (BES in-segment 0.08±0.45 mm; in-stent 0.13±0.46 mm). Although the time interval between 9 and 13 months may be too short to ascertain relevant differences in terms of late catch-up, the results reassuringly confirm the potent and sustained suppression of neointimal hyperplasia by the antiproliferative agent biolimus with a late lumen loss lower than with any early-generation DES in the setting of STEMI.[12,14,15] The long-term efficacy outcome of BES is also in line with previous reports comparing BES with sirolimus-eluting stent in an all comers trial with a continued benefit of BES throughout 5 years.[4] Conversely, late lumen loss observed with BMS used in this study was comparable to the one recorded in the paclitaxel-eluting stents versus BMSs in acute myocardial infarction (HORIZON AMI) trial[12] (in-segment/in-stent late loss BMS COMFORTABLE AMI, 0.71±0.75 mm/0.97±0.75 mm versus BMS HORIZON AMI, 0.59±0.64 mm/0.82±0.70 mm).

Limitation

Our results have to be interpreted in view of the following limitations. The trial indicated superiority on the primary composite outcome but was not powered to address individual components of efficacy or safety. Moreover, observed event rates were lower than anticipated. In view of the size of the observed treatment effect and results of previous trials, we consider it unlikely that estimates of efficacy would substantially differ in a larger patient cohort.

The inclusion of safety outcomes in the primary composite outcome is meaningful because cardiac death or TV-MI may be device related. Event rates of cardiac death or TV-MI were of similar magnitude as ischemia-driven target-lesion revascularization in our trial providing a similar weight of efficacy and safety parameters within the composite end point.

Conclusions

Our findings suggest that the use of BESs with biodegradable polymer in patients with STEMI is associated with continued clinical benefit in terms of MACEs beyond 1 year following routine discontinuation of dual antiplatelet therapy. Apart from the expected sustainability of a superior efficacy, BES was associated with a favorable safety profile as evidenced by lower rates of the composite of cardiac death or TV-MI as well as TV-MI throughout 2 years. The latter finding is hypothesis generating and requires validation in appropriately designed studies.

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Supplemental Material

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Biolimus-Eluting Stents With Biodegradable Polymer Versus Bare-Metal Stents in Acute Myocardial Infarction: Two-Year Clinical Results of the COMFORTABLE AMI Trial

Lorenz Räber, Henning Kelbæk, Masanori Taniwaki, Miodrag Ostojic, Dik Heg, Andreas Baumbach, Clemens von Birgelen, Marco Roffi, David Tüller, Thomas Engstrøm, Aris Moschovitis, Giovanni Pedrazzini, Peter Wenaweser, Ran Kornowski, Klaus Weber, Thomas F. Lüscher, Christian M. Matter, Bernhard Meier, Peter Jüni and Stephan Windecker
for the COMFORTABLE AMI Trial Investigators

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